Use of arterial spin-labeling characteristics as a predictor of glioma grade

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Purpose

Arterial spin labeling (ASL) is a relatively new but increasingly available technique in magnetic resonance imaging (MRI). It provides a measure of cerebral blood flow (CBF) by electromagnetically labelling inflowing arterial blood water to allow differentiation between static and flowing fluid.\textsuperscript{1,2}

Assessment of grade and recurrence of brain tumours is complex. Many MRI sequence characteristics are considered by the reporting radiologist including measures of cerebral perfusion using Dynamic Susceptibility contrast (DSC) and more recently using ASL.\textsuperscript{3,4}

DSC perfusion requires intravenous contrast administration and adequate timing of scan sequences. It is also a gradient echo technique therefore there may be associated problems with noise. There are also risks from the contrast agent itself (e.g. renal failure and nephrogenic systemic fibrosis). Warmuth et al found that DSC and ASL imaging yielded similar perfusion values when quantifying blood flow in brain tumours.\textsuperscript{5} Advantages of ASL are that it does not require contrast administration, is easily repeatable and provides a quantitative measure of cerebral perfusion.\textsuperscript{1,6}

Previous ASL studies show the technique's promise in improving diagnostic accuracy of glioma grading\textsuperscript{4,6,7} and that it correlates well with histopathologic vascular density\textsuperscript{8}. However, its reliability remains controversial and Roy et al suggested that it was not reliable in its current form\textsuperscript{9}. In this study, we have implemented a 3D pseudocontinuous ASL (pCASL) sequence which has an improved signal to noise ratio compared to previous versions due to improved labelling efficiency and improved readout.\textsuperscript{10,11}

Our long term goal is to use ASL for assessment of vascularity of gliomas, replacing the traditional DSC. This goal is significant because if the technique becomes routine in clinical practice it will both reduce costs and improve patient care by reducing the need for extrinsic contrast agents. It may also improve clinicians' ability to appropriately counsel patients prior to biopsy or perhaps reduce the requirement for biopsy. In our retrospective review we assess the relationship between pCASL-derived CBF values in gliomas and their biopsy-confirmed WHO grade.
Methods and materials

*Image data collection*

All scans were performed on a single GE Signa HDxt 3T scanner.

Potential cases were identified retrospectively by searching two computer systems for scans performed from July 2011 to September 2015. Firstly, the scanner database was searched to identify individuals that had received an ASL examination. This yielded 124 scans. Secondly, we searched radiological reports on the radiology information system with the following keywords: glioma, glioblastoma, astrocytoma, oligodendroglioma, or neoplasm. This yielded 152 scans.

*Image acquisition*

A stack of spiral, fast spin echo acquired images were prepared with pseudo-continuous arterial spin labelling and background suppression to measure whole brain perfusion quantitatively: TR = 6 s, echo spacing = 9.2 ms, post-labelling delay = 1.525 s, labelling duration = 1.5 s, eight interleaved spiral arms with 512 samples at 62.5 kHz bandwidth and 30 phase encoded 5mm thick slices, NEX = 3, units: ml/100 g/min).

*Laboratory data collection*

Experienced surgical pathologists performed the histopathologic evaluation. All tumours were proven on pathologic examination and classified in accordance with the WHO system of brain tumours. Tissue for histologic analysis was obtained following MRI scan and obtained during surgical resection or by stereotactic biopsy.

*Participants*

All cases (n=276) were reviewed in order to identify those with both biopsy/surgically-confirmed glioma and pCASL scan. Duplicate records were merged. Individuals were excluded for the following reasons: no glioma diagnosis, no biopsy or resection performed within 12 months of imaging, interim scanning without ASL with a change in the tumour prior to surgery, loss to follow-up, paediatric patients, no ASL or incomplete. After further review one patient was excluded from all analysis as the CBF was taken from the calvarium overlying the lesion rather than part of the tumour itself. Twenty-nine cases with ASL data met inclusion criteria.

*Qualitative/Semi-quantitative assessment*
Two radiologists reviewed each case and by reference to T1-weighted, T2-weighted, T2 FLAIR and post-contrast T1-weighted images the tumour was identified and co-registered to the quantified CBF maps. A qualitative score of lesion brightness was assigned based on the area of highest signal intensity. The score ranged from 1-4, to assess whether this correlated with WHO grades 1-4), where the following criteria were implemented:

1. - Lesion brightness \( \leq \) white matter (WM)
2. - Lesion brightness > WM but < grey matter (GM)
3. - Lesion brightness = GM
4. - Lesion brightness > GM

**Quantitative assessment**

A region of interest was placed on a single slice, encompassing the brightest part of the tumour by general consensus of the two radiologists. Additional regions of interest were also drawn contralaterally to act as a control region, one in the grey matter and one in the white matter. Average CBF values (measured in ml/100g/min) were extracted from lesion and control regions of interest in each individual.

**Statistical analysis**

The CBF of the lesion was standardised so that objective and subjective measures of CBF could be compared. This was done using the equation:

\[
\text{CBF standardised} = \frac{(\text{CBF lesion} - \text{CBF WM})}{(\text{CBF GM} - \text{CBF WM})}
\]

Thus a standardised CBF lesion value of 0 can be interpreted as having the same intensity as the patient's white matter, and a standardised CBF lesion value of 1 as having the same intensity as the patient's grey matter. A value of 2 would have twice the intensity of the difference between the grey matter and the white matter.

The level of agreement between standardised CBF lesion measurements versus radiologist ratings or WHO outcome scores was assessed graphically using boxplots, and a Jonckheere-Terpstra test was used test the alternative hypothesis that median standardised CBF lesion measurements increased with group score \(1<2<3<4\). Radiologist ratings and WHO outcome scores were cross-tabulated, and the degree of association between them compared using Cohen's weighted kappa statistic.

To investigate the ability of standardised CBF lesion measurements to predict having a high grade glioma (WHO grade 3 or 4), receiver operator characteristics (ROC) analyses
was performed and area under the curve (AUC) calculated with 95% DeLong confidence interval. Finally, to aid practical use, participants were dicotomised as having a CBF greater than 100mg/100g/min, or a radiologist rating of 4, in order to calculate the sensitivity, specificity, PPV and NPV (with 95% confidence intervals\textsuperscript{12}) of having a high grade glioma.

All statistical analysis was conducting using R 3.3.1\textsuperscript{13} with the following packages; ggplot2 2.1.0\textsuperscript{14}, epiR 0.9-79\textsuperscript{15}, and pROC 1.8.
Results

Biopsy or surgical specimen histological grading was performed within two months of MRI scan in all but four patients (87%). The longest interval between imaging and histological specimen was seven months.

The distribution of lesion CBF values for all subjects is displayed in Fig. 1 on page 9. Subjects diagnosed with a WHO grade 4 tended to receive higher radiological scores and had higher lesion CBF values.

Objective and subjective measures of CBF were compared using standardisation of the lesion relative to white and grey matter values. Standardised objective median CBF values progressively increased, from lowest in those with radiologist rating of 1 and 2, increasing slightly in those with a rating of 3, to reach their highest values in those with rating level 4 (Fig. 2 on page 9). However, there was overlap of whether the radiologist rating was a 3 or 4 at a similar CBF (non-standardised this was 50-75ml/100g/min). A Jonckheere-Terpstra test provided strong evidence (p < 0.001) there is a monotonic increase in the median of CBF measures by radiologist rating.

Next, we compared whether the objective and subjective measures of CBF correlated with tumour grade.

When comparing the radiologist score and WHO grade (Table 1 on page 15), we found that there was a 'fair' level of agreement. The weighted kappa was 0.30 (CI -0.03 to 0.63). However, the sample size was too small to rule out either a 'poor' or a 'good' level of agreement.

When comparing the standardised objective measure of CBF and WHO grade (Fig. 3 on page 10) we found a great deal of overlap in CBF between all tumour grades. The Jonckheere-Terpstra indicated some evidence of an increase in standardised CBF score by WHO grade (p = 0.006), but this appears to be for the highest WHO grade only.

The area under the curve (AUC) of the receiver operator curve (ROC) was 61% (95% CI 37% to 87%) using the raw CBF lesion values and 67% of standardised CBF (95% CI 43% to 91%). However, there was some evidence that the CBF of the lesion was able to predict a WHO grade of 4 (vs 1 to 3). The AUC of the ROC using the raw CBF lesion
scores was 75% (95% CI 56% to 94%), and using the standardised CBF was 80% (95% CI 62% to 97%).

The CBF lesion cut point that gave the best combination of sensitivity and specificity was:
For raw CBF lesion: 69 ml/100g/min gave 71% specificity and 77% sensitivity that the WHO grade would be a 3 or 4 (Fig. 4 on page 11). For standardised CBF lesion: 0.67 (two thirds of the difference between the white matter and grey matter CBFs) gave 65% specificity and 85% sensitivity that the WHO grade would be a 3 or 4 (Fig. 5 on page 12).

To aid practical use, further analyses were performed using a cutoff of CBF greater than 100mg/100ml/min and also a radiologist rating of 4 and the likelihood of high grade glioma (grade 3 or 4) (Table 2 on page 16).

**Discussion**

In our study we found that there was a high specificity and positive predictive value when CBF quantitative values were greater than 100mg/100ml/min and also when subjectively the radiologist rated the lesion as being a 4 (lesion CBF greater than grey matter CBF). The confidence intervals unfortunately are still large but suggest that ASL may prove to be a relatively simple and reliable method for radiologists to conclude that a tumour is high grade. This would aid therapeutic decisions and hopefully minimise morbidity and mortality with delayed or mis-diagnosis.

Lesions that demonstrate CBF which is similar or less than grey matter remain indeterminate as there is a large amount of overlap between tumour grades both objectively and subjectively.

**LIMITATIONS:**

The number of cases meeting criteria for further analysis was smaller than expected. In addition to the small numbers, by only focusing on a single slice, there was more susceptibility to noise. This could have been ameliorated by including a 3D volume but we were also attempting to make this a clinically applicable technique, so 2D slices were more feasible.

High grade gliomas are more common in adult patients meaning that a larger total sample size would be required to make conclusions about patients with lower grade tumours.

The scanner used for ASL imaging is a private research scanner and not generally used in primary review of brain tumours. Therefore there would be selection bias towards more complicated cases which required advanced imaging techniques.
The gold standard used was histological grade by surgical specimen or biopsy and this has its own limitations. Further review of cases of WHO Grade 2 glioma that had been rated as a 3 or 4 (higher grade) by the radiologist (n=4) was undertaken. Two patients had undergone biopsy and limited resection and subsequent scanning demonstrated the biopsy site was not concordant with the location of increased ASL signal. One patient is having ongoing follow-up (diagnosed 2014) and the other patient died within two months of imaging, suggesting that this was likely higher grade. The third patient had WHO Grade 2 Oligodendroglioma which was hypervascular, a known pitfall. The last lesion which had an CBF that was markedly increased at 307ml/100g/min (higher by almost twice) was actually misregistered and appeared to be in the calvarium overlying the lesion rather than part of the tumour itself (this case was excluded in the results).

IMAGING CHARACTERISTICS

There was characteristic morphology of the ASL in WHO grade 4 tumours which appeared like a 'lightbulb' in the shape of a 'banana' or 'donut' (Fig. 6 on page 13 Fig. 7 on page 14).

Lesions which were similar in brightness to grey matter or less bright were more difficult to define as the radiologist had to decide whether the tumour involved cortex or was just adjacent to oedematous cortex.

Approximately 50% of the cases had previous surgical resection of a glioma therefore there was alteration to normal anatomy which may have made evaluation more difficult.

TECHNICAL CONSIDERATIONS

The positioning of the ASL acquisition (superior to the mid cerebellum) did not allow reliable assessment of cerebellar lesions, due to signal dropout. Therefore ASL may not be the best modality to assess posterior fossa lesions.

In a number of our cases it was difficult to co-register the ASL data with T2 imaging for exact localisation of the tumour. Institutions using or planning to use the ASL technique should ensure that it is easy to co-register or routinely map the ASL with T2 imaging for ease of lesion identification.
**Fig. 1:** Summary graph of all measures. Participants are ordered sequentially along the x-axis according to their WHO score and ROI measurement of their lesion. Vertical black lines demarcate changes in WHO score (ordered from 1 to 4 for left to right). Each coloured vertical line represents the difference in CBF reading between the white matter (bottom of line) and grey matter (top of line) for an individual patient. The circles represent the CBF of each patient's lesion. The x-axis shows the radiologist rating for each patient.

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Fig. 2: Comparison of radiologist rating and standardised objective CBF of the tumour. Each dot on the figure represents a participant’s standardised CBF of the lesion (rounded to the nearest 0.2)

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Fig. 3: Comparison of standardised CBF and WHO grade of the tumour. Each dot on the figure represents a participant's standardised CBF of the lesion (rounded to the nearest 0.2)

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Fig. 4: Quantitative CBF cutpoint for prediction of a WHO grade 3 or 4 glioma. The distance = 200 - (sensitivity - specificity) represents the 'distance' from the perfect model (where 0 = perfect and 100 = uninformative).

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Fig. 5: Standardised CBF cutpoint for prediction of a WHO grade 3 or 4 glioma. The distance = 200 - (sensitivity - specificity) represents the 'distance' from the perfect model (where 0 = perfect and 100 = uninformative).

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**Fig. 6:** ASL in a high grade glioma with a characteristic 'banana' configuration

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Fig. 7: ASL in a high grade glioma with a characteristic 'donut' configuration

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Table 1: Comparison of WHO grade and radiologist ratings

<table>
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Table 2: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for CBF > 100mg/100ml/min compared to radiologist rating of 4

<table>
<thead>
<tr>
<th></th>
<th>CBF &gt; 100mg/100ml/min</th>
<th>Radiologist rating 4</th>
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<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>32 (14-55*)</td>
<td>45 (24-68*)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>86 (42-100*)</td>
<td>71 (29-96*)</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>88 (47-100*)</td>
<td>83 (52-98*)</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>29 (11-52*)</td>
<td>29 (10-56*)</td>
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* 95% confidence interval
Conclusion

ASL use for evaluation of glioma grade is promising. Objective and subjective measures of tumour CBF being greater than grey matter appears to have a high specificity and positive predictive value in predicting high grade tumours. However, the technique should still be used in the context of all MRI sequences to help suggest glioma grade. Ease and consistency of application of the ASL sequence requires reliable co-registration due to the amount of noise in the sequence. In addition, ASL may be helpful for problem solving or tumour recurrence imaging.

A way for the practicing radiologist to apply ASL to glioma grading would be: if the signal of the tumour is subjectively more intense than grey matter it is suggestive of a high grade glioma. Lesions that demonstrate CBF similar to grey matter or less are indeterminate as no association has been shown in this study. Alternately, using an objective threshold of ASL being greater than 100ml/100g/min is highly predictive of the lesion being high grade.
Fig. 6: ASL in a high grade glioma with a characteristic 'banana' configuration

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Fig. 7: ASL in a high grade glioma with a characteristic 'donut' configuration

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References

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References


